Ayinbuowan *et. al.* Babcock Univ. Med. J.2022 5(2):
https://doi.org/10.38029/ babcockunivmedj.xxxx
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

The current use of the artemisinin-based Combination Therapies in adult patients at a Tertiary Hospital, South-South Nigeria

Ayinbuowan SA[1,2], Opadeyi AO[1,2], Isah AO[1,2]

[1]Department of Clinical Pharmacology and Therapeutics, University of Benin, Benin-City, Nigeria
[2]Clinical Pharmacology and Therapeutics Unit, Department of Medicine, University of Benin Teaching Hospital, Benin-City, Nigeria

Submitted: 2nd June 2022
Accepted: 28th July 2022
Published:
ID: Orcid ID

Abstract
Objective: The antimalarial preferences, tolerability, and cost of the Artemisinin-based combination therapies (ACTs) among adult patients and caregivers are largely understudied despite being the recommended treatment for *Plasmodium falciparum*. We, therefore, evaluated antimalarial preferences, tolerability, and cost of the ACTs among adult patients attending the University of Benin Teaching Hospital, Nigeria.
Methods: This was a cross-sectional study conducted among adult patients and their caregivers at the University of Benin Teaching Hospital, Nigeria, using a semi-structured questionnaire. Their preferred antimalarial medication, previous use of antimalarial monotherapies, current ACT use; cost considerations, and adverse effects profile were sought.
Result: Six hundred respondents were recruited with a mean age of 41.4±16.3years and M/F ratio of 1.4. The majority (88.0 %), reported that they had between 1-5 episodes of malaria fever in a year. Only 28.2% received doctors' prescriptions while 85.8% purchased their antimalarial medications from a pharmacy. Sixty percent of the respondents used at least one ACT; mainly Artemether-Lumefantrine (AL) 312 (52.0%). Only 9.3% reported previous adverse effects with the ACTs with 4.0% of respondents discontinuing their medications. The mean (SD) cost of purchasing ACTs was 1,516.47±760.3 (3.65 USD) Naira.
Conclusion: This study showed adult patients' preference for the ACTs, especially Artemether-Lumefantrine despite some inclination towards antimalarial monotherapies and parenteral route. There was also a high rate of use of malaria presumptive treatment, but only a few reported adverse effects. There is a need to make ACTs affordable because the cost is still presently high for most Nigerians.

Keywords: Artemisinin, Adult, Antimalarial, Malaria, Nigeria

Plain English Summary

Artemisinin-based combination therapies (ACTs) are the choice medicines for malaria treatment. The preferences, tolerability, and cost of these ACTs are largely understudied. The antimalarial medication use, perception of effectiveness, tolerability, and cost of the ACTs among adult patients and their caregivers attending the University of Benin Teaching Hospital, Nigeria were studied. This information was obtained by administering questionnaires to the study participants. Six hundred respondents with an

Correspondence:
Ayinbuomwan, Stephen
Department of Clinical Pharmacology and Therapeutics, University of Benin, PMB 1151, Benin City, Edo State, Nigeria
+2348182499107, stephen.ayinbuomwan@uniben.edu

average age of 41.4±16.3years participated in this study. There were more female respondents in this study. The majority reported that they had between 1-5 episodes of malaria fever in a year. Less than one-third received doctors' prescriptions for antimalarial medication while the majority purchased their antimalarial medications from a pharmacy. More than half of the respondents used the ACTs which were mainly Artemether-lumefantrine. In the previous year, the commonly used nonACTs included herbal preparations, artemisinin injections, sulphadoxine-pyrimethamine, chloroquine, and quinine. Less than one-tenth reported previous adverse effects with the ACTs with 24 (4.0%) respondents discontinuing their medications. The average cost of purchasing ACTs was 1,516.47 Naira (760.3 USD). In conclusion, there was high malaria presumptive treatment despite the acceptance of the ACTs as choice antimalarial with a few reported adverse drug reactions. There is a need to make ACTs affordable because the cost is still presently high for most Nigerians.

Background

Malaria remains a major public health challenge, having roots extending deep within human communities (1). The progress attained in malaria control has largely been hinged on two main pillars; namely, the use of insecticides for targeting the anopheline mosquito vector, and the deployment of the artemisinin-based combination therapy (ACT) for prompt effective case management (2). Presently, these ACTs are the accepted global first-line therapies in the management of uncomplicated *falciparum* malaria as advocated by the WHO since 2001 (3) and embraced by member states experiencing the scourge of multi-drug resistant *Plasmodium falciparum* including Nigeria that adopted the ACTs policy in 2005 (4).

ACTs are antimalarial combination therapies that mirror the treatment approaches employed in the management of HIV, Leprosy, and Tuberculosis, to improve efficacy while simultaneously delaying the development of resistance. The concept involves the simultaneous use of two or more blood schizonticidal drugs with independent modes of action to improve efficacy and also delay the development of resistance to individual components of the combination (3). The ACTs adopted by the National antimalarial treatment policy contain an Artemisinin derivative (obtained from extracts of *Artemisia annua*) and any of the long-acting antimalarial agents such as lumefantrine, amodiaquine, mefloquine, or piperaquine (4). Thus, the recommended antimalarial agents in the Nigerian national policy are artemether-lumefantrine (AL) as the drug of choice, alternatives include artesunate-amodiaquine, artesunate-mefloquine, and dihydroartemisinin-piperaquine (4).

The world malaria report 2021 (5) indicated that the global progress against malaria has gradually leveled off since 2015. It highlighted an increase of 14 million more malaria cases and 47,000 more additional deaths in 2020 compared to 2019, with 24 nations recording an increase in malaria mortality. It also showed that Nigeria accounted for 27 % of the global malaria cases and 23 % of global malaria deaths (6). There are fears that the WHO global malaria strategy of reduction in malaria case incidence and mortality rate of at least 90% by 2030 may not be attainable (6). The emergence and spread of multi-drug resistant Plasmodium falciparum and resistant strains to insecticides have been recognized as the greatest impediments to malaria control especially in malaria-endemic countries (7). There is documentation of some degree of resistance to the artemisinins either as monotherapy or as ACTs in Western Cambodia, which has subsequently spread into countries of the Greater Mekong sub-region (8). Although these drugs are still effective within Sub-Saharan Africa, there are fears of the spread of these resistant strains as witnessed with chloroquine.

Studies in Nigeria had shown the acceptability of the ACTs soon after their introduction and recently (9, 10, 11). However, despite the efficacy attributed to the use of these medicines, a proportion of the patients and healthcare providers were still using non-ACT and herbal remedies for the management of malaria due to high-cost considerations, the number of tablets required, and tolerability issues (9, 10, 11).

The need to ensure and sustain increased acceptance of the ACTs to reduce the malaria burden prompted several interventions such as the affordable medicines malaria facility project to reduce the cost of production, reduce the cost to end-users and encourage higher use of the medicines even after the project was completed (12, 13). Furthermore, a national cohort event monitoring of the ACTs and other studies showed that the ACTs were fairly well tolerated buttressing the recommendation of artemether-lumefantrine as the first choice antimalarial agent for use in Nigerians (14, 15, 16).

The health-seeking behavior of individuals has been defined as any action undertaken by people who perceive themselves to have a health

problem or to be ill to find an appropriate remedy (17). This can be influenced by an interplay of factors ranging from recognition of disease presentations, availability and cost of treatment services, perceived effectiveness, and tolerability to medications. Thus, an understanding of the perception and behavior of individuals may be far-reaching in determining the success of specific control measures. The burden of disease ascribed to malaria in the last WHO report for Nigeria (5) makes it imperative still to evaluate the health-seeking behavior of Nigerian adults as it pertains to the use, preferences, tolerability, and cost of ACTS.

This is due to earlier research (11) that had shown healthcare providers' personal preferences and there was thus, a need to evaluate if adult patients in the same locality without a medical background would have a different perspective. This study, therefore, set out to determine antimalarial medication use, perception of effectiveness, tolerability, as well as the cost of the ACTs among adult patients attending the Consultant Out-patient Department in the University of Benin Teaching Hospital (UBTH), South-South, Nigeria.

Methodology

A cross-sectional study was carried out among adult patients who visited the Consultant Out-Patient Department (COPD) of the University of Benin Teaching Hospital (UBTH), South-South, Nigeria between March and May 2021. It is a federal government-owned tertiary healthcare facility with approximately 850-bed space capacity serving the communities in the surrounding five local government areas of Edo State and adjoining states of Delta, Kogi, and Ondo.

The UBTH Consultant Out-Patient Department (COPD) is a constellation of internal medicine specialists' clinics attending to adult patients with various medical conditions. An average of 100 patients are seen daily across the various specialties.

Participants/Sampling Technique

Adult patients (greater than 18 years) attending the COPD as well as their caregivers were approached to participate in the survey. Convenient sampling was employed to recruit those who consented to the study until the estimated sample size was achieved.

Study instrument

A semi-structured questionnaire was administered to the study participants. Those who were not educated were assisted by the research assistants in completing the questionnaire. The study instrument was pilot tested and necessary adjustments were made to the items in the questionnaire before final deployment to the participants. Content and face validity was carried out by experts in the field. The questionnaire was divided into four sections. Section A involves the demographics of the participants; section B deals with their malaria treatment behavior and antimalarial preferences; section C deals with adverse drug reactions and tolerability to the artemisinin-based combination therapy, and lastly, section D involves the cost of purchasing the ACTs.

Sample Size determination

The sample size for this survey was calculated with the aid of the OpenEpi software (18). A prevalence of 50% was utilized as the preferred antimalarial medication of choice by the respondents. With a 95% confidence level, a minimum sample size of 384 was estimated. The final sample size was increased to 600 in keeping with WHO recommendation on investigating drug use in a health facility (19).

Statistical Analysis

The Microsoft Excel (2016) spreadsheet was utilized for initial data entering, while the final analysis was done with the aid of the Statistical Package for Social Sciences (SPSS, version 21, Chicago, USA). Data were presented descriptively using means and percentage distribution.

Results

A total of 600 people were recruited for the study. There were more females 346 (57.7%) and the mean age (SD) was 41.4 ± 16.3 years. More than half were married 323 (53.5%). The majority of the respondents were workers 367 (61.2%), followed by traders/farmers 89 (14.8%). Concerning the number of episodes of malaria fever, the majority 528 (88.0 %), reported that they had between 1-5 episodes of malaria fever in a year while 10 (1.7%) respondents had over 10 episodes per year. Close to half of the population 256 (42.7%) did not undertake malaria parasite tests before treatment as shown in Table 1. Furthermore, only 139 (23.2%) would undertake the Widal's agglutination test in addition to testing for malaria parasitemia.

More than half of the respondents reported fever 343 (57.2%), generalized weakness 256 (42.7%), headache 248 (41.3), bitter taste 168 (28.0), and joint pains 109 (18.2) as symptoms suggestive of malaria.

Table 1: Socio-demographic and characteristics of the respondents (n=600)

Characteristics	Frequency (%)
Age	
<40	337 (56.6)
41- 60	169 (28.4)
> 60	89 (15.0)
Missing	5 (0.8)
Sex	
Male	249 (41.5)
Female	346 (58.2)
Missing	5 (0.8)
Occupation	
Workers	367 (61.2)
Students	86 (14.3)
Trader/Farmer	89 (14.8)
Retired	36 (6.0)
Missing	22(3.7)
Marital Status	
Married	323 (53.8)
Single	212 (35.3)
Divorced	12 (2.0)
Widowed	35 (5.8)
No response	18 (3.0)
Frequency of malaria episodes in a year	
1-5 episodes	528 (88.0)
6-10 episodes	41(6.8)
Over 10 episodes	10 (1.7)
No episodes	16 (2.7)
Missing	9 (1.5)
Investigation – malaria parasite test	
Yes	190 (31.7)
No	256 (42.7)
Sometimes	148 (24.7)
Missing	6 (1.0)

Regarding their last treatment for malaria, the majority of the respondents 326 (54.3%) had received treatment for malaria in the preceding 1-6 months, and 102 (17.0%) had been treated within the 4 weeks before this study.

More than half of the respondents 360 (60.0 %) used artemisinin-based combination therapy in the management of their malaria. Artemether-lumefantrine (AL) was the most utilized in this survey, 312 (52.0%), particularly brands such as Lonart DS® 132 (22.0%), amatem® 83 (13.8%), coartem® 70 (11.7%). Other ACTs used by the respondents include dihydroartemisinin-piperaquine 20 (3.3%) and artesunate-amodiaquine 15 (2.5%). Most of the respondents 515 (85.8%) purchased their antimalarial medications from a pharmacy/chemist, and 62 (10.3%) from the hospital. The most preferred route for antimalarial medication was the oral route 426 (71.0%), followed by the injections 95 (15.8%). This is

In addition, 334 (55.7%) respondents did not purchase antimalarial medicines without a recommendation, and the recommendation was obtained mostly from doctors 169 (28.2%) and pharmacists 91 (15.2%), nurses 45 (7.5%), sellers 8 (1.3%), while 5 (0.8%) obtained a recommendation from their friends and 16 (2.7%).

Table 2: Antimalarial practice and type of medication

Characteristics	Frequency (%)
Last malaria treatment	
Less than a month	102 (17.0)
1-6 months	326 (54.3)
7-12 months	99 (16.5)
Over a year ago	29 (4.8)
Cannot recall	8 (1.3)
Missing	36 (6.0)
Type of antimalarial medication	
ACT	360 (60.0)
NON- ACT	70 (11.7)
Any recommended antimalarial	64 (10.7)
Can't recall	25 (4.2)
Missing	81 (13.5)
Specific Types of antimalarial used	
Artemether-Lumefantrine (Lonart DS®)	132 (22.0)
Artemether-Lumefantrine (Amatem®)	83 (13.8)
Artemether-Lumefantrine (Coartem®)	70 (11.7)
Artemether-Lumefantrine (Lokmal®)	6(1.0)
Artemether-Lumefantrine (Lumartem®)	3(0.5)
Artemether-Lumefantrine (Uplufa®)	1(0.2)
Artemether-Lumefantrine	17 (2.8)
Dihydroartemisinin-Piperaquine (P-alaxin®)	20 (3.3)
Artesunate-Amodiaquine (Artequine®)	9(1.5)
Artesunate-Amodiaquine (Camosunate®)	6 (1.0)
Artemisinin-Piperaquine (Artequick®)	1(0.2)
Any ACT	12 (2.0)
Injection***	22 (3.7)
Artesunate	17(2.8)
Chloroquine	15 (2.5)
Quinine	6(1.0)
Sulphadoxine-Pyrimethamine (Fansidar®)	3 (0.5)
Sulphadoxine-Pyrimethamine (Maloxine®)	2(0.3)
Sulphadoxine-Pyrimethamine (Amalar®)	1(0.2)
Herbal drugs	3(0.5)
Proguanil hydrochloride (Paludrine®)	1(0.2)
Any antimalarial recommended	64 (10.7)
Can't recall	25 (4.2)
Missing	81 (13.5)
Place of purchase of medication	
Pharmacy/Chemist	515(85.8)
Hospital	62(10.3)
Hawkers	3(0.5)
Gifted medicine	1(0.2)
Missing	19 (3.2)
The preferred route for antimalarial medication	
Oral route	426(71.0)
Injections	95(15.8)
No preference	25(4.2)
Missing	54(9.0)

***Injections are alpha-beta arteether/ artemether, ACT: Artemisinin-based Combination Therapy

Following thematic analysis, the reasons for choosing ACTs by a proportion of the respondents were: effectiveness 100 (16.7%), fast action 20 (3.3%), affordability 16 (2.7%), recommendation 22 (3.7%), accessibility 6 (1.0%), convenient dosing regimen 7 (1.2%), and

minimal adverse effects 3 (0.5%). A high proportion of respondents 393 (65.5%) admitted to using paracetamol during the treatment of malaria. Other concomitant medicines include antibiotics 255 (42.5%), multivitamins 109 (18.2%) and hematinics 80 (13.3%).

In the previous year, the non-ACTs used include herbal preparations 98 (16.3%), artemisinin injections 71 (11.8%), sulphadoxine-pyrimethamine 39 (6.5%), chloroquine 34 (5.7%), and quinine 24(4.0 %). Although 50 (8.3%) respondents preferred these non-ACTs to the ACTs, 43(86.0%) gave the following reasons for their preference: effectiveness 24 (55.8%), fast action 9 (20.9%), convenience 5(11.6%) minimal ADR 3 (7.0%), less costly 2(4.7%) and 8(18.6%) gave no response.

A minority of the respondents 56 (9.3%) reported previous adverse effects with the ACTs. Only which were mostly from AL 21(37.5%). Twenty-four (42.9%) persons could not recall the ACT name but reported adverse effects. The adverse effects for AL were majorly general administration and site disorders 11 (52.3%), gastrointestinal disorders 4 (19.0%), while for AA, the adverse effects were also majorly general administration and site disorders 5 (83.3%), skin and subcutaneous disorders 1(16.9%) as seen in Table 3. Twenty-four (4.0%) respondents admitted to having discontinued their medications following adverse effects while 5 (0.8%) claimed to have been hospitalized due to an adverse effect.

Table 3: Adverse drug reactions associated with the ACTs and systems affected

Drug	n=56(%)	System Organ Classification	n (%)
Artemether-Lumenfatrine	21(37.5)	General administration and site disorders	11(52.3)
		Gastrointestinal Disorders	4(19.0)
		Psychiatric	2(9.5)
		Nervous system	2(9.5)
		Skin and subcutaneous	1(4.8)
		Cardiac disorders	1(4.8)
Artesunate-Amodiaquine	6(10.7)	General administration and site disorders	5(83.3)
		Skin and subcutaneous tissue disorders	1(16.7)
Dihyrdoartemisin-Piperaquine	5 (8.9)	Gastrointestinal disorders	2 (40)
		Hepatobiliary disorders	1(20)
		General administration and site disorder-	1(20)
		Not stated	1(20)
Can't recall particular ACT	24(42.9)	General administration and site disorder-	7(29.2)
		Gastrointestinal disorders-	6(25)
		Skin and subcutaneous tissue disorders	2(8.3)
		Cardiac disorders-	2 (8.3)
		Nervous disorders	2 (8.3)
		Not stated	6 (25)

The mean (SD) cost of purchasing ACTs was ₦1,516.47±760.3 (3.65 USD), ranging from ₦200 to ₦5000 (0.48 -12.04 USD), and the median (IQR) was ₦1,450.0 (₦1000- ₦1940). Furthermore, 103 (17.2%) reported that cost influenced their choice of ACTs.

Discussion

Artemether-Lumefantrine (AL) was the most utilized antimalarial by the respondents in this study in line with the National Antimalarial Policy which adopted AL as the drug of choice in treating uncomplicated malaria, corroborating similar findings in Sub-Saharan Africa (20, 21).

The ACTs were the most preferred antimalarials for the treatment of uncomplicated malaria as

they were preferred by over half of the study participants. Our finding was similar to that of Adisa et al (22) in Ibadan conducted three years into the change of the National Antimalarial Policy (NAP) in 2005. Ezenduka et al (23) in Enugu in a recent survey also found ACT utilization to be 72.7% among randomly selected outlets. Again, a higher level of 93.7% was observed in another study (24) conducted in a University community. However, the majority of the study population obtained their ACTs from the hospital, while only a few were involved in self-medication These similarities in the level of ACT acceptance after 15 years of change of the NAP may reflect the sustained progress in the drive toward promoting ACT acceptance among the populace.

Artemether-Lumefantrine (AL), although available as a fixed-dose formulation is taken twice daily (25) unlike the other recommended ACT combinations which have a daily dosing regimen. However, it is widely available over the counter in different generic formulations in an attempt to address both administrative and cost challenges both in adults and children thus making it an attractive treatment option. The reasons given by the respondents in this study for the choice of AL were mostly due to its perceived effectiveness, fast onset of action, affordability, recommendation, and accessibility.

Only 32 % of the respondents were confident that they performed a blood film or rapid diagnostic test before taking antimalarial therapy despite the majority 88% having had between 1-5 episodes of malaria in the previous year corroborating the findings of Akanbi et al (26) and Ajonina et al (27). This high level of presumptive diagnosis is especially seen among health professionals, particularly in high transmission areas who assume that they can easily differentiate malaria fevers from other fevers (28, 29). Clinical diagnosis of malaria has a very low specificity and is likely to promote over-treatment, eventually aiding the wastage of limited resources and straining the already weak healthcare system. This may also promote irrational use of antibiotics as concomitant medications as highlighted in this study (42.5%), with the likelihood of increasing selection pressure for the emergence and spread of antibiotic-resistant bacteria. To address this unhealthy development, the WHO recommends confirmatory parasitologic diagnosis to identify patients with malaria, and thus, promote rational use of antimalarial medicines (25).

About half of the respondents in this study sought recommendations before purchasing their antimalarials while only about one-third received prescriptions from doctors. This finding is consistent with other reports from Cameroon, Kenya, and Ghana in which high levels of self-medication have been reported (27, 30, 31). Self-medication is practiced globally and it is driven by disease conditions, educational status, gender, and age. WHO encourages self-medication only in minor ailments to decrease the cost of treatment and allow health professionals to concentrate on more serious health conditions (32). This approach while addressing the unavailability of health personnel and over-crowding in health facilities may further encourage incorrect self-diagnosis and irrational drug use, especially in adults who consider malaria as a minor illness.

Most of the reported adverse effects in this study were associated with the most commonly used ACT (artemether-lumefantrine) similar to other pharmacovigilance studies in Ghana and Malawi (33, 34). The most commonly reported ADRs were general administration and site disorders such as generalized weakness, headache, and dizziness, corroborating the findings of Ndagije et al (35) in Uganda. Almost all the ADRs associated with AA were generalized weakness and dizziness. Estes et al (36) reported that fatigue associated with AA may be linked to the amodiaquine (AQ) component, which is due to the development of transient toxic myopathy and/ or neuropathy that resolves completely following completion or discontinuation of the drug.

The mean cost of the ACTs in this survey was ₦1,516.47 (3.65 USD). This finding was similar to the systematic review of cost analysis studies of control interventions from Sub-Saharan Africa, Asia, and South America (37). This review put the median financial cost of treating uncomplicated malaria at 5.84 USD with a range between 2.36 USD to 23.65 USD. The ACTs, although effective is still very costly and largely unaffordable despite previously mentioned interventions (12) and especially in a resource-poor setting like Nigeria, where the cost of healthcare is largely from out-of-pocket payment. The World Bank documents that 58% of Nigerians receive 1.25 USD per day as their take-home pay (38). The implication of this is that patients are more likely to switch to cheaper but less effective antimalarials as well as the use of herbal agents. This may also explain the patient's preference for the non-ACTs in the previous year of this study where they utilized chloroquine 34 (5.7%), sulphadoxine-pyrimethamine 39 (6.5%), quinine 24(4.0%) and herbal preparations 98 (16.3%). Although Nigeria had launched the National Health Insurance

Scheme in an attempt to offer a necessary buffer to this cost challenge (39), the majority of the citizens are yet to benefit and continue to pay out of pocket.

Limitations
The limitations of this survey include the use of convenience sampling in recruiting the respondents. It was also difficult to disaggregate pharmacy outlets from the chemist because a majority of the respondents could not differentiate them. Lastly, we recognize the likelihood of recall bias while filling the questionnaire. These limitations however did not impact negatively this survey.

Conclusion
In conclusion, this study found a high acceptance for the ACTs. In addition, artemether-lumefantrine (AL) was the respondents' preferred antimalaria in treating uncomplicated malaria as recommended by the National antimalarial Policy. Although the experienced adverse reactions were largely tolerable, there is a need to educate the populace on the importance of prompt and spontaneous reporting of adverse drug reactions. There is an urgent need to address the cost of procurement of ACTs to make them affordable to the very poor in society. This will to a large extent discourage preference for the use of non-ACTs and antimalarial monotherapies that are available in the open market. In addition, the government may have to partner with pharmaceutical companies and donor agencies to encourage domestic production of the ACTs and strengthen malaria treatment in the country.

List of Abbreviations
ADR: Adverse Drug Reaction
AL: Artemether-Lumefantrine
COPD: Consultant Outpatient Clinic
HIV: Human Immunodeficiency Virus
WHO: World Health Organization
ACT: Artemisinin-combination therapy
UBTH: University of Benin Teaching Hospital

Declarations
Ethical approval and consent to participate
We obtained ethical approval from the institutions' research and ethics committee (UBTH ADM/E22/A/VOL.VII/14831018) before commencing the study. Respondents who agreed to participate gave their written informed consent. All information obtained was kept securely and not shared with third parties. Confidentiality of the provided information was ensured throughout the study.

Consent for publication
The authors consented to the publication of the work under the creative commons CC Attribution. Non-commercial 4.0 license.

Availability of data and materials
The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests
The authors have no competing interests to declare.

Funding Statement
The authors are the sole funders of the research.

Acknowledgments
Nil.

Authors' contributions
All authors were involved in the conceptualization of the study; data collection, data entry, analysis and interpretation; literature review; and manuscript drafting and revision.

References
1. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, Battle KE, Moyes CL, Henry A, Eckhoff PA, Wenger EA. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature. 2015 Oct;526(7572):207-11. https://doi.org/10.1038/nature15535
2. WHO. Guidelines for malaria 2021. Geneva, Switzerland.
3. World Health Organization. Antimalarial drug combination therapy. Report of a WHO technical consultation. Geneva: World Health Organization. 2001 Apr 4;33.
4. Federal Ministry of Health. National antimalarial treatment policy, 2010. Abuja, Nigeria.
5. WHO. World Malaria Report 2021. Geneva, World Health Organization 2021.
6. World Health Organization. Global technical strategy for malaria 2016-2030. World Health Organization; 2015 Nov 4.
7. WHO. Malaria: Key facts 2022. World Health Organization 2022. https://www.who.int/news-room/fact-sheets/detail/malaria (Accessed May 2022)

8. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, Sreng S, Anderson JM, Mao S, Sam B, Sopha C. Tracking Resistance to Artemisinin Collaboration (TRAC). 2014. Spread of artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med.;371(5):411-23.
9. Chukwuocha UM, Nwakwuo GC, Mmerole I. Artemisinin-based combination therapy: knowledge and perceptions of patent medicine dealers in Owerri Metropolis, Imo State, Nigeria and implications for compliance with the current malaria treatment protocol. Journal of Community health. 2013 Aug;38(4):759-65. https://doi.org/10.1007/s10900-013-9676-y
10. Balogun ST, Jibrin J, Tahir R, Bassi PU, Balogun FA, Fehintola FA. Perceptions of artemisinin-based combination therapies among Nigerian women seven years after adoption as first-line drugs. Am J Res Commun. 2013.
11. Ayinbuomwan AS, Opadeyi AO, Isah AO. Artemisinin-based antimalarial combination therapy amongst healthcare professionals in a tertiary facility in south-south Nigeria: preferences, tolerability, and cost considerations. Research Journal of Health Sciences. 2022 May 18;10(2):112-20. https://doi.org/10.4314/rejhs.v10i2.5
12. Tougher S, Ye Y, Amuasi JH, Kourgueni IA, Thomson R, Goodman C, Mann AG, Ren R, Willey BA, Adegoke CA, Amin A. Effect of the Affordable Medicines Facility—malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data. The Lancet. 2012 Dec 1;380(9857):1916-26. https://doi.org/10.1016/S0140-6736(12)61732-2
13. Tougher S, Hanson K, Goodman C. What happened to anti-malarial markets after the Affordable Medicines Facility-malaria pilot? Trends in ACT availability, price, and market share from five African countries under the continuation of the private sector co-payment mechanism. Malaria journal. 2017 Dec;16(1):1-8. https://doi.org/10.1186/s12936-017-1814-z
14. Ayinbuomwan AS, Isah AO. Safety and Tolerability Profile of Artemisinin-Based Antimalarial Combination Therapy in Adult Patients in Benin City, Nigeria. West African Journal of Pharmacology and Drug Research. 2014;29:25-9.
15. Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of Tropical Medicine. 2015 May 28;2015. https://doi.org/10.1155/2015/189232
16. Bassi PU, Osakwe AI, Suku C, Kalat M, Elagbaje C, Isah A, Ayinbuomwan S, Wammanda RD, Bob-Okon II, Ambe J, Mava Y. Cohort event monitoring of patients treated for uncomplicated malaria with artemisinin-based combination therapies in selected hospitals and community pharmacies in Nigeria. Nigerian Postgraduate Medical Journal. 2016 Oct 1;23(4):172. https://doi.org/10.4103/1117-1936.196246
17. Ward H, Mertens TE, Thomas C. Health seeking behaviour and the control of sexually transmitted diseases. Health Policy and planning. 1997 Jan 1;12(1):19-28. https://doi.org/10.1093/heapol/12.1.19
18. Sullivan KM, Dean A. OPENEPI: A Web-based epidemiologic and statistical calculator for Public Health. 2009; 124: 471–474. https://doi.org/10.1177/003335490912400320
19. World Health Organization. How to investigate drug use in health facilities: selected drug use indicators. World Health Organization; 1993.
20. Mazigo HD, Obasy E, Mauka W, Manyiri P, Zinga M, Kweka EJ, Mnyone LL, Heukelbach J. Knowledge, attitudes, and practices about malaria and its control in rural northwest Tanzania. Malaria Research and Treatment. 2010;2010. https://doi.org/10.4061/2010/794261
21. Amponsah AO, Vosper H, Marfo AF. Patient-related factors affecting adherence to antimalarial medication in an urban estate in Ghana. Malaria Research and Treatment. 2015;2015. https://doi.org/10.1155/2015/452539
22. Adisa R, Fakeye TO, Dike D. Evaluation of adverse drug reactions to artemisinin-based combination therapy in a Nigeria university community. Tropical Journal of Pharmaceutical Research. 2008 Jun 23;7(2):937-44. https://doi.org/10.4314/tjpr.v7i2.14680
23. Ezenduka CC, Ogbonna BO, Ekwunife OI, Okonta MJ, Esimone CO. Drugs use pattern for uncomplicated malaria in medicine retail

outlets in Enugu urban, southeast Nigeria: implications for malaria treatment policy. Malaria Journal. 2014 Dec;13(1):1-0. https://doi.org/10.1186/1475-2875-13-243
24. Monday BB, Victoria UC, Ogochukwu AM. Level of Antimalarial Drug Utilization Amongst Teaching and Non-Teaching Staff of University of Port Harcourt, Rivers State, Nigeria. International Journal of Infectious Diseases and Therapy 2022; 7(1): 1-7
25. World Health Organization. WHO guidelines for malaria, 3 June 2022. World Health Organization; 2022.
26. Akanbi OM, Odaibo AB, Afolabi KA, Ademowo OG. Effect of self-medication with antimalarial drugs on malaria infection in pregnant women in South-Western Nigeria. Medical Principles and Practice. 2005;14(1):6-9. https://doi.org/10.1159/000081915
27. Ajonina MU, Apinjoh TO, Atanga SN, Ayim M, Akomoneh EA, Ajonina C. Practices regarding the use of antimalarial medications among inhabitants of the Buea health district, southwestern Cameroon: implications towards malaria treatment policy. Journal of Health, Medicine & Nursing. 2015;21:86-95.
28. Bamgboye EA, Amoran OE, Yusuf OB. Self-medication practices among workers in a tertiary hospital in Nigeria. African journal of medicine and medical sciences. 2006 Dec 1;35(4):411-5.
29. Chen JY, Tse EY, Lam TP, Li DK, Chao DV, Kwan CW. Doctors' personal health care choices: A cross-sectional survey in a mixed public/private setting. BMC Public Health. 2008 Dec;8(1):1-7. https://doi.org/10.1186/1471-2458-8-183
30. Watsierah CA, Jura WG, Raballah E, Kaseje D, Abong'o B, Ouma C. Knowledge and behaviour as determinants of anti-malarial drug use in a peri-urban population from malaria holoendemic region of western Kenya. Malaria Journal. 2011 Dec;10(1):1-7. https://doi.org/10.1186/1475-2875-10-99
31. Buabeng KO, Duwiejua M, Dodoo AN, Matowe LK, Enlund H. Self-reported use of anti-malarial drugs and health facility management of malaria in Ghana. Malaria journal. 2007 Dec;6(1):1-6. https://doi.org/10.1186/1475-2875-6-85
32. Galato D, Galafassi LD, Alano GM, Trauthman SC. Responsible self-medication: a review of the process of pharmaceutical attendance. Brazilian Journal of Pharmaceutical Sciences. 2009;45:625-33. https://doi.org/10.1590/S1984-82502009000400004
33. Dodoo AN, Fogg C, Nartey ET, Ferreira GL, Adjei GO, Kudzi W, Sulley AM, Kodua A, Ofori-Adjei D. Profile of adverse events in patients receiving treatment for malaria in urban Ghana: a cohort-event monitoring study. Drug safety. 2014 Jun;37(6):433-48. https://doi.org/10.1007/s40264-014-0164-9
34. Kalilani-Phiri LV, Lungu D, Coghlan R. Knowledge and malaria treatment practices using artemisinin combination therapy (ACT) in Malawi: a survey of health professionals. Malaria journal. 2011 Dec;10(1):1-7. https://doi.org/10.1186/1475-2875-10-279
35. Ndagije HB, Nambasa V, Manirakiza L, Kusemererwa D, Kajungu D, Olsson S, Speybroeck N. The burden of adverse drug reactions due to artemisinin-based antimalarial treatment in selected Ugandan health facilities: an active follow-up study. Drug safety. 2018 Aug;41(8):753-65. https://doi.org/10.1007/s40264-018-0659-x
36. Estes ML, Ewing-Wilson D, Chou SM, Mitsumoto H, Hanson M, Shirey E, Ratliff NB. Chloroquine neuromyotoxicity. Clinical and pathologic perspective. The American journal of medicine. 1987 Mar 1;82(3):447-55. https://doi.org/10.1016/0002-9343(87)90444-X
37. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions-a systematic review. Malaria journal. 2011 Dec;10(1):1-4. https://doi.org/10.1186/1475-2875-10-337
38. World Bank. World development indicators 2015. The World Bank; 2015 Apr. https://doi.org/10.1596/978-1-4648-0440-3
39. Fadare JO, Adeoti AO, Desalu OO, Enwere OO, Makusidi AM, Ogunleye O, Sunmonu TA, Truter I, Akunne OO, Godman B. The prescribing of generic medicines in Nigeria: knowledge, perceptions, and attitudes of physicians. Expert review of pharmacoeconomics & outcomes research. 2016 Sep 2;16(5):639-50. https://doi.org/10.1586/14737167.2016.1120673